METHODS FOR IMPROVING RESPONSE TO ANTI-LIF ANTIBODY TREATMENT IN INDIVIDUALS WITH CANCER

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims the benefit of European Application Serial Number 18382431.7, filed Jun. 18, 2018, and European Application Serial Number 19382131.1, filed Feb. 22, 2019, all of which are hereby incorporated by reference in their entireties.

BACKGROUND

[0002] Leukemia inhibitory factor (LIF) is a member of the interleukin-6 (IL-6) family of cytokines. Based on the known physiological activities of LIF, clinical features of LIF deficiency, and nonclinical studies of LIF expression in healthy tissues and tumors, inhibition of LIF is expected to be well tolerated and to result in anti-tumor efficacy in a range of solid tumors, including but not limited to non-small cell lung cancer (NSCLC), pancreatic cancer, ovarian cancer and glioblastoma multiforme (GBM).

[0003] One problem facing clinicians when treating cancer with target specific therapeutics, is that not all tumors may be responsive to a given target specific therapeutic. Even for tumor types known to express LIF or the LIF receptor there is significant heterogeneity amongst individual tumors. Additionally, not all tumors that express LIF or LIF receptor may respond similarly, thus there is a need for effective methods to determine individuals that may most benefit from treatment with an anti-LIF therapeutic antibody.

SUMMARY

[0004] The present disclosure relates to methods of treating cancer in individuals comprising administering a therapeutic anti-LIF antibody to those individuals most likely to respond to said antibody, and methods of determining which individuals are most likely to respond to a therapeutic anti-LIF antibody. Patients with tumors or cancers that exhibit expression of LIF or the LIF receptor at an mRNA or protein level that exceeds a reference level, as described herein, can be effectively treated with a LIF therapeutic antibody. Additionally, several non-LIF biomarkers are described that can determine individuals that would benefit from treatment with a therapeutic anti-LIF antibody. These non-LIF biomarkers can be used alone or together with an assay that measures a LIF or a LIF receptor level. Non-LIF biomarkers include immunomodulatory molecules that indicate an immunosuppressive signature, these include, the presence of immunosuppressive cell types, immunosuppressive cytokines, or immunosuppressive chemokines. It is envisioned that determining a LIF or LIF receptor level together with an immunosuppressive signature will increase the predictive power of a method of determining treatment with a therapeutic anti-LIF antibody.

[0005] In one aspect, described herein, is a method of treating an individual with cancer with a therapeutic anti-leukemia inhibitory factor (LIF) antibody comprising determining a level of LIF that exceeds a reference level in a biological sample from the individual, and administering a therapeutic amount of the anti-LIF antibody to the individual when the level of LIF is greater than the reference level of LIF. In certain embodiments, the therapeutic anti-LIF antibody comprises: an immunoglobulin heavy chain complementarity determining region 1 (VH-CDR1) comprising the amino acid sequence set forth in any one of SEQ ID NOs: 1-3; an immunoglobulin heavy chain complementarity determining region 2 (VH-CDR2) comprising the amino acid sequence set forth in any one of SEQ ID NOs: 4 or 5; an immunoglobulin heavy chain complementarity determining region 3 (VH-CDR3) comprising the amino acid sequence set forth in any one of SEQ ID NOs: 6-8; an immunoglobulin light chain complementarity determining region 1 (VL-CDR1) comprising the amino acid sequence set forth in any one of SEQ ID NOs: 9 or 10; an immunoglobulin light chain complementarity determining region 2 (VL-CDR2) comprising the amino acid sequence set forth in any one of SEQ ID NOs: 11 or 12; and an immunoglobulin light chain complementarity determining region 3 (VL-CDR3) comprising the amino acid sequence set forth in SEQ ID NO: 13. In certain embodiments, the therapeutic anti-LIF antibody comprises an immunoglobulin heavy chain variable region comprising at least 85%, 90%, 95%, 97%, 98%, 99%, or 100% identity to SEQ ID NOs: 14, 15, 17 or 38 and an immunoglobulin light chain variable region comprising at least 85%, 90%, 95%, 97%, 98%, 99%, or 100% identity to SEQ ID NO: 18-21. In certain embodiments, the therapeutic anti-LIF antibody comprises an immunoglobulin heavy chain region comprising at least 85%, 90%, 95%, 97%, 98%, 99%, or 100% identity to SEQ ID NOs: 30-33 or 39, and an immunoglobulin light chain region comprising at least 85%, 90%, 95%, 97%, 98%, 99%, or 100% identity to SEQ ID NOs: 34-37. In certain embodiments, the therapeutic anti-LIF antibody is an IgG antibody comprising two immunoglobulin heavy chains and two immunoglobulin light chains. In certain embodiments, the level of LIF is a LIF protein level and determining the level comprises performing at least one assay that detects LIF protein or receiving the results of at least one assay that detects LIF protein. In certain embodiments, the at least one assay comprises immunohistochemistry. In certain embodiments, the reference level is about 1%, 2%, 3%. 4%, 5%, 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 35%, or 50% of cells staining positive with an anti-LIF antibody.

[0006] In certain embodiments, the reference level is an IHC-score of about 100. In some embodiments, the reference level is an IHC-score of about 1 to about 300. In some embodiments, the reference level is an IHC-score of about 1 to about 30, about 1 to about 60, about 1 to about 90, about 1 to about 120, about 1 to about 150, about 1 to about 180, about 1 to about 210, about 1 to about 240, about 1 to about 270, about 1 to about 300, about 30 to about 60, about 30 to about 90, about 30 to about 120, about 30 to about 150, about 30 to about 180, about 30 to about 210, about 30 to about 240, about 30 to about 270, about 30 to about 300, about 60 to about 90, about 60 to about 120, about 60 to about 150, about 60 to about 180, about 60 to about 210, about 60 to about 240, about 60 to about 270, about 60 to about 300, about 90 to about 120, about 90 to about 150, about 90 to about 180, about 90 to about 210, about 90 to about 240, about 90 to about 270, about 90 to about 300, about 120 to about 150, about 120 to about 180, about 120 to about 210, about 120 to about 240, about 120 to about 270, about 120 to about 300, about 150 to about 180, about 150 to about 210, about 150 to about 240, about 150 to about 270, about 150 to about 300, about 180 to about 210, about